Application No.: 10/010942 Docket No.: ELN-002

AMENDMENTS TO THE CLAIMS

This listing of the claims will replace all prior versions, and listings, of claims in this application.

1. **(Original)** A humanized immunoglobulin light chain comprising (i) variable region complementarity determining regions (CDRs) from the 3D6 immunoglobulin light chain variable region sequence set forth as SEQ ID NO:2, and (ii) a variable framework region from a human acceptor immunoglobulin light chain sequence, provided that at least one framework residue is substituted with the corresponding amino acid residue from the mouse 3D6 light chain variable region sequence, wherein the framework residue is selected from the group consisting of:

(a) a residue that non-covalently binds antigen directly;

(b) a residue adjacent to a CDR;

(c) a CDR-interacting residue; and

(d) a residue participating in the VL-VH interface.

2. **(Original)** A humanized immunoglobulin heavy chain comprising (i) variable region complementarity determining regions (CDRs) from the 3D6 immunoglobulin heavy chain variable region sequence set forth as SEQ ID NO:4, and (ii) a variable framework region from a human acceptor immunoglobulin heavy chain, provided that at least one framework residue is substituted with the corresponding amino acid residue from the mouse 3D6 heavy chain variable region sequence, wherein the framework residue is selected from the group consisting of:

(a) a residue that non-covalently binds antigen directly;

(b) a residue adjacent to a CDR;

(c) a CDR-interacting residue; and

(d) a residue participating in the VL-VH interface.

3. **(Original)** The light chain of claim 1, wherein a CDR-interacting residue is identified by modeling the 3D6 light chain based on the solved structure of 1CR9.

4. **(Original)** The light chain of claim 1, wherein a CDR-interacting residue is identified by modeling the 3D6 light chain based on the solved structure of 1NLD.

5. **(Original)** The heavy chain of claim 2, wherein a CDR-interacting residue is identified by modeling the 3D6 heavy chain based on the solved structure of 1OPG.

6. **(Original)** A humanized immunoglobulin light chain comprising (i) variable region complementarity determining regions (CDRs) from the 3D6 immunoglobulin light chain variable region sequence set forth as SEQ ID NO:2, and (ii) a variable framework region from a human acceptor immunoglobulin light chain sequence, provided that at least one framework residue is substituted with the corresponding amino acid residue from the mouse 3D6 light chain variable region sequence, wherein the framework residue is a residue capable of affecting light chain variable region conformation or function as identified by analysis of a three-dimensional model of the 3D6 immunoglobulin light chain variable region.

7. **(Original)** A humanized immunoglobulin heavy chain comprising (i) variable region complementarity determining regions (CDRs) from the 3D6 immunoglobulin heavy chain variable region sequence set forth as SEQ ID NO:4, and (ii) variable framework region from a human acceptor immunoglobulin heavy chain, provided that at least one framework residue is substituted with the corresponding amino acid residue from the mouse 3D6 heavy chain variable region sequence, wherein the framework residue is a residue capable of affecting heavy chain variable region conformation or function as identified by analysis of a three-dimensional model of the 3D6 immunoglobulin heavy chain variable region.

8. **(Original)** The light chain of claim 6, wherein the framework residue is selected from the group consisting of a residue capable of interacting with antigen, a residue proximal to the antigen binding site, a residue capable of interacting with a CDR, a residue adjacent to a CDR, a residue within 6 Å of a CDR residue, a canonical residue, a vernier zone residue, an interchain packing residue, a rare residue, and a glycoslyation site residue on the surface of the structural model.

9. **(Previously Presented)** The heavy chain of claim 7, wherein the framework residue is selected from the group consisting of a residue capable of interacting with antigen, a residue proximal to the antigen binding site, a residue capable of interacting with a CDR, a

residue adjacent to a CDR, a residue within 6 Å of a CDR residue, a canonical residue, a vernier zone residue, an interchain packing residue, a rare residue, and a glycoslyation site residue on the surface of the structural model.

10. **(Previously Presented)** The light chain of claim 6, wherein the framework residue is identified by modeling the 3D6 light chain based on the solved structure of 1CR9.

11. **(Previously Presented)** The light chain of claim 6, wherein the frame work residue is identified by modeling the 3D6 light chain based on the solved structure of 1NLD.

12. **(Previously Presented)** The heavy chain of claim 7, wherein the framework residue is identified by modeling the 3D6 heavy chain based on the solved structure of 1OPG.

13. **(Original)** A humanized immunoglobulin light chain comprising (i) variable region complementarity determining regions (CDRs) from the 3D6 immunoglobulin light chain variable region sequence set forth as SEQ ID NO:2, and (ii) a variable framework region from a human acceptor immunoglobulin light chain, provided that at least one framework residue selected from the group consisting of L1, L2, L36 and L46 (Kabat numbering convention) is substituted with the corresponding amino acid residue from the mouse 3D6 light chain variable region sequence.

14. **(Original)** A humanized immunoglobulin heavy chain comprising (i) variable region complementarity determining regions from the 3D6 heavy chain variable region sequence set forth as SEQ ID NO:4, and (ii) a variable framework regions from a human acceptor immunoglobulin heavy chain, provided that at least one framework residue selected from the group consisting of H49, H93 and H94 (Kabat numbering convention) is substituted with the corresponding amino acid residue from the mouse 3D6 heavy chain variable region sequence.

15. **(Previously Presented)** The light chain of claim 1, wherein the human acceptor light chain is of the subtype kappa II (Kabat convention).

16. **(Previously Presented)** The heavy chain of claim 2, wherein the human acceptor heavy chain is of the subtype III (Kabat convention).

17. **(Original)** The light chain of claim 15, wherein the human acceptor light chain is selected from the group consisting of Kabat ID 019230, Kabat ID 005131, Kabat ID 005058, Kabat ID 005057, Kabat ID 005059, Kabat ID U21040 and Kabat ID U41645.

18. **(Original)** The light chain of claim 15, wherein the human acceptor light chain is Kabat ID 019230.

19. **(Original)** The heavy chain of claim 16, wherein the human acceptor heavy chain is selected from the group consisting of Kabat ID 045919, Kabat ID 000459, Kabat ID 000553, Kabat ID 000386 and Kabat ID M23691.

20. **(Original)** The heavy chain of claim 16, wherein the human acceptor heavy chain is Kabat ID 045919.

21. **(Previously Presented)** The light chain of claim 1, wherein at least one rare human framework residue is substituted with an amino acid residue which is common for human variable light chain sequences at that position.

22. **(Previously Presented)** The light chain of claim 1, wherein at least one rare human framework residue is substituted with a corresponding amino acid residue from a germline variable light chain sequence.

23. **(Original)** The light chain of claim 22, wherein the germline variable light chain sequence is selected from the group consisting of A1, A17, A18, A2, and A19.

24. **(Previously Presented)** The heavy chain of claim 2, wherein at least one rare human framework residue is substituted with an amino acid residue which is common for human variable heavy chain sequences at that position.

25. **(Previously Presented)** The heavy chain of claim 2, wherein at least one rare human framework residue is substituted with a corresponding amino acid residue from a germline variable heavy chain sequence.

26. **(Original)** The heavy chain of claim 25, wherein the germline variable heavy chain sequence is selected from the group consisting of VH3-48, VH3-23, VH3-7, VH3-21 and VH3-11.

27. **(Original)** The heavy chain of claim 25, wherein the germline variable heavy chain sequence is VH3-23.

28. **(Previously Presented)** The light chain of claim 21, wherein the rare framework residue is selected based on occurrence at that position in less than 10% of human light chain variable region sequences in the light chain variable region subgroup, and the common residue is selected based on an occurrence at that position in greater than 50% of sequences in the light chain variable region subgroup.

29. **(Previously Presented)** The heavy chain of claim 24, wherein the rare framework residue is selected based on occurrence at that position in less than 10% of human heavy chain variable region sequences in the heavy chain variable region subgroup, and the common residue is selected based on an occurrence at that position in greater than 50% of sequences in the heavy chain variable region subgroup.

30. **(Original)** A light chain comprising the complementarity determining regions (CDRs) and variable region framework residues L1, L2, L36 and L46 (Kabat numbering convention) from the monoclonal antibody 3D6 light chain, wherein the remainder of the light chain is from a human immunoglobulin.

31. **(Original)** A heavy chain comprising the complementarity determining regions (CDRs) and variable framework residues H49, H93 and H94 (Kabat numbering convention) from the monoclonal antibody 3D6 heavy chain, wherein the remainder of the heavy chain is from a human immunoglobulin.

32. **(Previously Presented)** A humanized immunoglobulin comprising a light chain selected from the group consisting of:

(a) a light chain comprising variable region complementarity determining regions (CDRs) from the 3D6 immunoglobulin light chain variable region sequence set forth as SEQ ID NO:2; and comprising variable framework regions from a human acceptor immunoglobulin light chain sequence, provided that at least one framework residue is substituted with the corresponding amino acid residue from the mouse 3D6 light chain variable region sequence, wherein the framework residue is selected from the group consisting of
(i) a residue that non-covalently binds antigen directly;
(ii) a residue adjacent to a CDR;
(iii) a CDR-interacting residue; and
(iv) a residue participating in the VL-VH interface;

(b) a light chain comprising variable region complementarity determining regions (CDRs) from the 3D6 immunoglobulin light chain variable region sequence set forth as SEQ ID NO:2, and comprising variable framework regions from a human acceptor immunoglobulin light chain sequence, provided that at least one framework residue is substituted with the corresponding amino acid residue from the mouse 3D6 light chain variable region sequence, wherein the framework residue is a residue capable of affecting light chain variable region conformation or function as identified by analysis of a three-dimensional model of the variable region;

(c) a light chain comprising variable region complementarity determining regions (CDRs) from the 3D6 immunoglobulin light chain variable region sequence set forth as SEQ ID NO:2, and a variable framework regions from a human acceptor immunoglobulin light chain, provided that at least one framework residue selected from the group consisting of L1, L2, L36 and L46 (Kabat numbering convention) is substituted with the corresponding amino acid residue from the mouse 3D6 light chain variable region sequence; and

(d) a light chain comprising the complementarity determining regions (CDRs) and variable region framework residues L1, L2, L36 and L46 (Kabat numbering

convention) from the monoclonal antibody 3D6 light chain, wherein the remainder of the light chain is from a human immunoglobulin;

and a heavy chain selected from the group consisting of:

(a) heavy chain comprising variable region complementarity determining regions (CDRs) from the 3D6 immunoglobulin heavy chain variable region sequence set forth as SEQ ID NO:4, and comprising variable framework regions from a human acceptor immunoglobulin heavy chain, provided that at least one framework residue is substituted with the corresponding amino acid residue from the mouse 3D6 heavy chain variable region sequence, wherein the framework residue is selected from the group consisting of:

(i) a residue that non-covalently binds antigen directly;

(ii) a residue adjacent to a CDR;

(iii) a CDR-interacting residue; and

(iv) a residue participating in the VL-VH interface;

(b) a heavy chain comprising variable region complementarity determining regions (CDRs) from the 3D6 immunoglobulin heavy chain variable region sequence set forth as SEQ ID NO:4, and comprising variable framework regions from a human acceptor immunoglobulin heavy chain, provided that at least one framework residue is substituted with the corresponding amino acid residue from the mouse 3D6 heavy chain variable region sequence, wherein the framework residue is a residue capable of affecting heavy chain variable region conformation or function as identified by analysis of a three-dimensional model of the variable region;

(c) a heavy chain comprising variable region complementarity determining regions from the 3D6 heavy chain variable region sequence set forth as SEQ ID NO:4, and a variable framework regions from a human acceptor immunoglobulin heavy chain, provided that at least one framework residue selected from the group consisting of H49, H93 and H94 (Kabat numbering convention) is substituted with the corresponding amino acid residue from the mouse 3D6 heavy chain variable region sequence; and

(d) a heavy chain comprising the complementarity determining regions (CDRs) and variable framework residues H49, H93 and H94 (Kabat numbering convention)

from the monoclonal antibody 3D6 heavy chain, wherein the remainder of the heavy chain is from a human immunoglobulin;

or an antigen binding fragment of said immunoglobulin.

33. **(Original)** The immunoglobulin or antigen binding fragment of claim 32, which specifically binds to beta amyloid peptide (Aβ) with a binding affinity of at least 10^7 M^{-1}.

34. **(Original)** The immunoglobulin or antigen binding fragment of claim 32, which specifically binds to beta amyloid peptide (Aβ) with a binding affinity of at least 10^8 M^{-1}.

35. **(Original)** The immunoglobulin or antigen binding fragment of claim 32, which specifically binds to beta amyloid peptide (Aβ) with a binding affinity of at least 10^9 M^{-1}.

36. **(Original)** The immunoglobulin or antigen binding fragment of claim 32, wherein the heavy chain isotype is γ1.

37. **(Original)** The immunoglobulin or antigen binding fragment of claim 32, which binds to both soluble beta amyloid peptide (Aβ) and aggregated Aβ.

38. **(Previously Presented)** The immunoglobulin or an antigen binding fragment of claim 37, wherein the soluble beta amyloid peptide (Aβ) is disaggregated Aβ.

39. **(Original)** The immunoglobulin or antigen binding fragment of claim 32, which mediates phagocytosis of beta amyloid peptide (Aβ).

40. **(Original)** The immunoglobulin or antigen binding fragment of claim 32, which crosses the blood-brain barrier in a subject.

41. **(Original)** The immunoglobulin or antigen binding fragment of claim 32, which reduces both beta amyloid peptide (Aβ) burden and neuritic dystrophy in a subject.

42.-61. **(Cancelled)**

62. **(Previously Presented)** A pharmaceutical composition comprising the immunoglobulin or an antigen binding fragment of claim 32 and a pharmaceutical carrier.

63.-164. **(Cancelled)**

165. **(Previously Presented)** The light chain of claim 8, wherein the framework residue is identified by modeling the 3D6 light chain based on the solved structure of 1CR9.

166. **(Previously Presented)** The light chain of claim 8, wherein the frame work residue is identified by modeling the 3D6 light chain based on the solved structure of 1NLD.

167. **(Previously Presented)** The heavy chain of claim 9, wherein the framework residue is identified by modeling the 3D6 heavy chain based on the solved structure of 1OPG.

168. **(Previously Presented)** The light chain of claim 6, wherein the human acceptor light chain is of the subtype kappa II (Kabat convention).

169. **(Previously Presented)** The light chain of claim 13, wherein the human acceptor light chain is of the subtype kappa II (Kabat convention).

170. **(Previously Presented)** The heavy chain of claim 7, wherein the human acceptor heavy chain is of the subtype III (Kabat convention).

171. **(Previously Presented)** The heavy chain of claim 14, wherein the human acceptor heavy chain is of the subtype III (Kabat convention).

172. **(Previously Presented)** The light chain of claim 168, wherein the human acceptor light chain is selected from the group consisting of Kabat ID 019230, Kabat ID 005131, Kabat ID 005058, Kabat ID 005057, Kabat ID 005059, Kabat ID U21040 and Kabat ID U41645.

173. **(Previously Presented)** The light chain of claim 169, wherein the human acceptor light chain is selected from the group consisting of Kabat ID 019230, Kabat ID 005131, Kabat ID 005058, Kabat ID 005057, Kabat ID 005059, Kabat ID U21040 and Kabat ID U41645.

174. **(Previously Presented)** The light chain of claim 168, wherein the human acceptor light chain is Kabat ID 019230.

175. **(Previously Presented)** The light chain of claim 169, wherein the human acceptor light chain is Kabat ID 019230.

176. **(Previously Presented)** The heavy chain of claim 170, wherein the human acceptor heavy chain is selected from the group consisting of Kabat ID 045919, Kabat ID 000459, Kabat ID 000553, Kabat ID 000386 and Kabat ID M23691.

177. **(Previously Presented)** The heavy chain of claim 171, wherein the human acceptor heavy chain is selected from the group consisting of Kabat ID 045919, Kabat ID 000459, Kabat ID 000553, Kabat ID 000386 and Kabat ID M23691.

178. **(Previously Presented)** The heavy chain of claim 170, wherein the human acceptor heavy chain is Kabat ID 045919.

179. **(Previously Presented)** The heavy chain of claim 171, wherein the human acceptor heavy chain is Kabat ID 045919.

180. **(Previously Presented)** The light chain of claim 6, wherein at least one rare human framework residue is substituted with an amino acid residue which is common for human variable light chain sequences at that position.

181. **(Previously Presented)** The light chain of claim 13, wherein at least one rare human framework residue is substituted with an amino acid residue which is common for human variable light chain sequences at that position.

182. **(Previously Presented)** The light chain of claim 6, wherein at least one rare human framework residue is substituted with an corresponding amino acid residue from a germline variable light chain sequence.

183. **(Previously Presented)** The light chain of claim 13, wherein at least one rare human framework residue is substituted with a corresponding amino acid residue from a germline variable light chain sequence.

184. **(Currently Amended)** The light chain of claim 182, wherein the germline variable light chain sequence is selected from the group consisting of A1, A17, A18, A2, and A19.

185. **(Previously Presented)** The light chain of claim 183, wherein the germline variable light chain sequence is selected from the group consisting of A1, A17, A18, A2, and A19.

186. **(Previously Presented)** The heavy chain of claim 7, wherein at least one rare human framework residue is substituted with an amino acid residue which is common for human variable heavy chain sequences at that position.

187. **(Previously Presented)** The heavy chain of claim 14, wherein at least one rare human framework residue is substituted with an amino acid residue which is common for human variable heavy chain sequences at that position.

188. **(Previously Presented)** The heavy chain of claim 7, wherein at least one rare human framework residue is substituted with a corresponding amino acid residue from a germline variable heavy chain sequence.

189. **(Previously Presented)** The heavy chain of claim 14, wherein at least one rare human framework residue is substituted with a corresponding amino acid residue from a germline variable heavy chain sequence.

190. **(Previously Presented)** The heavy chain of claim 188, wherein the germline variable heavy chain sequence is selected from the group consisting of VH3-48, VH3-23, VH3-7, VH3-21 and VH3-11.

191. **(Previously Presented)** The heavy chain of claim 189, wherein the germline variable heavy chain sequence is selected from the group consisting of VH3-48, VH3-23, VH3-7, VH3-21 and VH3-11.

192. **(Previously Presented)** The heavy chain of claim 188, wherein the germline variable heavy chain sequence is VH3-23.

193. **(Previously Presented)** The heavy chain of claim 189, wherein the germline variable heavy chain sequence is VH3-23.

194. **(Previously Presented)** The light chain of claim 180, wherein the rare framework residue is selected based on occurrence at that position in less than 10% of human light chain variable region sequences in the light chain variable region subgroup, and the common residue is selected based on an occurrence at that position in greater than 50% of sequences in the light chain variable region subgroup.

195. **(Previously Presented)** The light chain of claim 181, wherein the rare framework residue is selected based on occurrence at that position in less than 10% of human light chain variable region sequences in the light chain variable region subgroup, and the common residue is selected based on an occurrence at that position in greater than 50% of sequences in the light chain variable region subgroup.

196. **(Previously Presented)** The heavy chain of claim 186, wherein the rare framework residue is selected based on occurrence at that position in less than 10% of human heavy chain variable region sequences in the heavy chain variable region subgroup, and the common residue is selected based on an occurrence at that position in greater than 50% of sequences in the heavy chain variable region subgroup.

197. **(Previously Presented)** The heavy chain of claim 187, wherein the rare framework residue is selected based on occurrence at that position in less than 10% of human heavy chain variable region sequences in the heavy chain variable region subgroup, and the common residue is selected based on an occurrence at that position in greater than 50% of sequences in the heavy chain variable region subgroup.

198. **(Previously Presented)** A pharmaceutical composition comprising the immunoglobulin or an antigen binding fragment of claim 33 and a pharmaceutical carrier.

199. **(Previously Presented)** A pharmaceutical composition comprising the immunoglobulin or an antigen binding fragment of claim 34 and a pharmaceutical carrier.

200. **(Previously Presented)** A pharmaceutical composition comprising the immunoglobulin or an antigen binding fragment of claim 35 and a pharmaceutical carrier.

201. **(Previously Presented)** A pharmaceutical composition comprising the immunoglobulin or an antigen binding fragment of claim 36 and a pharmaceutical carrier.

202. **(Previously Presented)** A pharmaceutical composition comprising the immunoglobulin or an antigen binding fragment of claim 37 and a pharmaceutical carrier.

203. **(Previously Presented)** A pharmaceutical composition comprising the immunoglobulin or an antigen binding fragment of claim 38 and a pharmaceutical carrier.

204. **(Previously Presented)** A pharmaceutical composition comprising the immunoglobulin or an antigen binding fragment of claim 39 and a pharmaceutical carrier.

205. **(Previously Presented)** A pharmaceutical composition comprising the immunoglobulin or an antigen binding fragment of claim 40 and a pharmaceutical carrier.

206. **(Previously Presented)** A pharmaceutical composition comprising the immunoglobulin or an antigen binding fragment of claim 41 and a pharmaceutical carrier.